IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant: Charlie RICCI, et al.

Title: METHODS FOR TREATING ENDOLEAKS DURING ENDOVASCULAR REPAIR OF ABDOMINAL AORTIC ANEURYSMS

Appl. No.: 09/954,789

Filing Date: 9/12/2001

Examiner: S. Sharareh

Art Unit: 1617

CERTIFICATE OF MAILING
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Esther Lily C. Esguerra
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September 30, 2005
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SUBSTITUTE APPEAL BRIEF

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

37 C.F.R. § 41.37(c)(1)(i) REAL PARTY IN INTEREST

The real party in interest in this application is MicroTherapeutics, Inc. (MTI), assignee of the entire right, title, and interest to this application by virtue of an assignment from the inventors to MTI in the grandparent application, U.S. Patent No. 6,203,779.

37 C.F.R. § 41.37(c)(1)(ii) RELATED APPEALS AND INTERFERENCES

There are no related appeals and/or interferences relating to this application.

37 C.F.R. § 41.37(c)(1)(iii) STATUS OF CLAIMS

Claims 1-19 were in the filed application.

Claims 1-15 were canceled with a preliminary amendment submitted with the filing of this application leaving Claims 16-19 as the only claims remaining in this application at that time.

Claim 16 was subsequently amended on July 15, 2002 in response to the Office Action mailed March 13, 2002. In addition, Claims 17-19 were canceled and new Claims 20-29 added.

Claim 16 was further amended on January 20, 2004 in response to the Office Action mailed October 21, 2003. In addition, new Claims 30-32 were added.

Claims 16 and 20-32 remain pending in the application and stands rejected under 35 U.S.C. 103(a) over McCrory (U.S. Patent No. 5,951,599), in view of Chuter *et al.* ((2000) *J. Vasc. Surg.* 31:122-33), May *et al.* ((2000) *J. Vasc. Surg.* 32:124-129) and Evans *et al.* (U.S. Patent No. 5,695,480), all of which are of record in the application.

This rejection of Claims 16 and 20-32 is appealed, herein.

A copy of the Claims on Appeal is provided in the attached Claims Appendix.

37 C.F.R. § 41.37(c)(1)(iv) STATUS OF AMENDMENTS

All amendments, except the amendment filed on July 21, 2004 have been entered by the United States Patent and Trademark Office (herein, "the Patent Office").

37 C.F.R. § 41.37(c)(1)(v) SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 16 is directed to a kit of parts for sealing leaks resulting from vascular surgery. Specification at, *e.g.*, page 7, line 26 – page 8, line 24 and page 20, line 14 – page 21, line 14.

The first component of this kit is a fluid composition which forms a coherent mass in the presence of blood which mass adheres to the vascular surface and/or the surface of the endovascular prosthesis. Specification at, *e.g.*, page 6, lines 1-6 and page 20, lines 20-25. This fluid comprises a biocompatible solvent and biocompatible polymer and is recited in Appellants' specification at, *e.g.*, page 6, lines 1-16 and page 8, lines 1-6.

The second component of this kit is a catheter suitable delivering the fluid composition to an endoleak site formed from endovascular repair of an aneurysm. Specification at, *e.g.*, page 8, line 7-8.

The third component is a catheter suitable for delivering an endovascular prosthesis to the aneurysm. Specification at, *e.g.*, page 8, lines 9-10.

The fourth component is an endovascular prosthesis comprising a *stent-graft*[1] capable of inhibiting but not completely arresting blood flow into the abdominal aortic aneurysm due to the presence of one or more endoleaks. Support for the fourth component of the kit can be found at, *e.g.*, page 18, lines 1-14; page 25, lines 1-4 and 16-18; page 26, lines 15-19; and page 27, lines 8-10. However, it should be noted that the timing of this support in this application, and the applications from which it depends, is an issue in the instant Appeal, and is discussed at *I, infra.*

Dependent claims 20 and 21 are drawn to a kit comprising a particular biocompatible polymer. Support can be found in the specification at, *e.g.*, page 9, line 16 – page 11, line 14.

[1] Because of the relevance to the issue on Appeal, of the similar-looking terms *stent* and *stent-graft*, these terms will often appear in italics.

Dependent claims 22 and 23 are drawn to a kit comprising a particular biocompatible solvent. Support can be found in the specification at, *e.g.*, page 12, lines 1-9.

Dependent claims 24-31 are drawn to a kit comprising a particular biocompatible contrast agent, selected from a water insoluble contrast agent (claims 25-27) and a water soluble contrast agent (claims 28 and 29). Support can be found in the specification at, *e.g.*, page 11, lines 15-29. Claims 30 and 31 are drawn to a contrast agent dissolved in saline. Specification at, *e.g.*, page 20, lines 6-10.

Dependent claim 32 is drawn to a kit for sealing particular endoleaks arising from incomplete sealing a the interface of the aortic wall and the end of the prosthesis or from defects within the prosthesis. Support can be found in the specification at, *e.g.*, page 9, lines 6-15.

37 C.F.R. § 41.37(c)(1)(vi) GROUNDS FOR REJECTION TO BE REVIEWED ON APPEAL

The primary issue for consideration by the Honorable Board of Patent Appeals and Interferences is whether to reverse or affirm the rejection of Claims 16 and 20-32 under 35 U.S.C. §103(a) over McCrory (U.S. Patent 5,951,599), in view of Chuter *et al.* ((2000) *J. Vasc. Surg.* 31:122-33), May *et al.* ((2000) *J. Vasc. Surg.* 32:124-129) and Evans *et al.* (U.S. Patent 5,695,480).[2] There is a subissue which concerns whether of not the Chutter and May references are available as prior art against these claims, in view of the disclosures in this application and its predecessors.

[2] In the Office Action of April 1, 2004 at page 6, the Patent Office issued a new obviousness rejection over Evans *et al.* in view of Chuter *et al.* However, since Evans does not teach the use of stent-grafts (page 6) the new rejection relies on Chuter *et al.* to supply the alleged teaching that stents and stent-grafts are interchangeable. Accordingly, the arguments made, herein, with be equally applicable to the new obviousness rejection, which is based on only a subset of the references cited above.

37 C.F.R. § 41.37(c)(1)(vii) ARGUMENT

Appellants respectfully submit that the outstanding obviousness rejection should be withdrawn for the following reasons:

I. The combination of the cited references (*i.e.*, McCrory, in view of Chuter *et al.*, May *et al.* and Evans *et al.*) can not render obvious the claimed invention because neither Chuter *et al.* nor May *et al.* constitute prior art. These articles each are predated by this application's "grandparent," which satisfies the written description requirement of 35 U.S.C. § 112, with respect to all of the claims on appeal, and in particular to their recitation of the use of *stent grafts.*

II. The combination of the cited references (*i.e.*, McCrory, in view of Chuter *et al.*, May *et al.* and Evans *et al.*) does not produce the claimed invention because:

A. Neither Chuter *et al.* nor May *et al.*, taken individually or together, establish that *stents* and *stent grafts* are interchangeable devices for endovascular repair; and

B. One skilled in the art would not be motivated to combine Chuter *et al.* and/or May *et al.* with McCrory.

These arguments are further discussed, below.

I. Neither Chuter *et al.* nor May *et al.* constitute prior art against the claimed invention

The instant application is a divisional of U.S. Patent Application Serial No. 09/528,656, now U.S. Patent No. 6,475,466, which, in turn, is a continuation-in-part of U.S. Patent Application Serial No. 09/273,120, now U.S. Patent No. 6,203,779. The '120 "grandparent" application has a filing date of March 19, 1999, which is prior to the publication dates of both the cited Chuter *et al.* and May *et al.* references, which were published in 2000.

The Patent Office alleges that Applicants are not entitled to the March 19, 1999 priority date of the grandparent application because "March 2000 is the earliest time the Applicants appear to have envisioned the use of stent-grafts in their kits"[3]. However, this assertion is incorrect. All of the claims under appeal find 35 U.S.C. § 112-satisfying support in the '120 application. The rejection concedes this support with respect to all aspects of these claims save their recitation of "stent grafts." Thus, a showing of support for these other aspects of the claimed invention need not be belabored.

The '120 application is drawn to methods of treating endoleaks during endovascular repair (see throughout, including the title). As described in the '120 specification, "[a]ny endoleak can be treated in the methods of this invention including endoleaks arising, for example, from incomplete sealing between the endovascular prosthesis and the aortic wall . . . " (column 4, lines 64-66). The specification further teaches that ". . . endovascular repair of such aneurysms involves the introduction of an endovascular prosthesis into the abdominal aortic aneurysm which is an art recognized procedure described, for example, by Parodi[17]" (column 9, lines 34-37).

Parodi (reference 17, column 2, lines 13-16), in turn, recites in its very title "Endovascular AAA *Stent Grafts*: Technology, Training and Proper Patient Selection" (emphasis added) and describes the nature and use of *stent grafts*. This reference was incorporated by reference in its entirety into the '120 application.

Additionally, Example 2 of the '120 application describes the use of a Wallgraft (Schneider, Boston Scientific, Boston MA), which is a *stent-graft*. In fact, Example 2 described the use of Wallgraft that was intentionally perforated to produce a "graft defect" to demonstrate the efficacy of the particular described embodiment of the invention (see, *e.g.*, column 12, lines 46-48 and column 13, lines 22-27).

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[3] See, footnotes 1 and 2 bridging pages 2 and 3 of the Office Action of April 21, 2004.

Accordingly, the '120 application, upon which the instant application is based, clearly contemplated the use of *stent-grafts* as an endovascular prosthesis. It is, therefore, incorrect for the Office to assert that the 1999-filed '120 application failed to contemplate *stent-grafts* in its kits.

Since the instant application is entitled to the 1999 filing date of the '120 application for the combination of each and every element of the kits claimed in claims 16 and 20-32, and since the filing date of the '120 application predates the Chuter *et al.* and May *et al.* references, they cannot constitute prior art against the claimed invention. Withdrawal of this rejection is, therefore, requested. As an aside, to this point in the prosecution of this application, there has been no request by the Examiner that any material from the Parodi article, which was incorporated by reference into the '120 specification, be directly recited in the present specification. If, in the opinion of the Honorable Board, this direct recitation would facilitate allowance of the claims, Appellants will be quick to oblige.

II. The combination of the cited references (*i.e.*, McCrory, in view of Chuter *et al.*, May *et al.* and Evans *et al.*) does not produce the claimed invention.

A. Neither Chuter *et al.* nor May *et al.*, taken individually or together, establish that stents and stent grafts are interchangeable devices for endovascular repair.

While, for reasons discussed above, the Chuter *et al.* and May *et al.* references are not available to support an obviousness rejection against the pending claims, there would be an independent reason to overturn the obviousness rejection based on these references, even if they were available.

The outstanding obviousness rejection[4] appears to rely on the combination of a U.S. Patent (*i.e.*, McCrory), which teaches vascular occlusive systems involving a *stent* and a polymeric composition; two clinical research studies (*i.e.*, Chuter *et al.* and May *et al.*), which report the clinical outcomes of endovascular aneurysm repair, involving stent-grafts, in

[4] Office Action of February 14, 2003 at page 2.

populations of patients as allegedly teaching the equivalence of *stents* and *stent* grafts; and Evans *et al.*, a reference disclosing a kit for endovascular aneurysm repair.[5]

The rejection is improper because, neither Chuter *et al.* nor May *et al.*, taken separately or together, teach, suggest, or imply, that *stents* and *stent-grafts* are equivalent devices for endovascular repair. To the contrary, Chuter *et al.* at page 123 states that "[m]ost of the patients in this series underwent treatment with a custom-made *stent graft*, that consisted of two Z *stents* and a tubular, or tapered, sleeve of conventional fabric" (references omitted, emphasis added). The paper proceeds to discuss the particular characteristics of the *proximal stent* and *distal stent* (*Id.*), which comprise the stent-graft. This language affirmatively shows that, at least according to the Chuter *et al.* paper, stent-grafts *comprise* stents. Chuter *et al.* clearly do not teach that the *stent-grafts* are synonymous with, or equivalent to, *stents*.

The paper of May *et al.* appears to be drawn exclusively to the use of stent-grafts (using the terminology, "prosthetic devices"). The paper is replete with such terms as "graft-related," "graft failure," and "graft-related deaths" (*e.g.*, at page 127), while endovascular aneurysm repair using simple stents, without a graft component, does not appear to be within the scope of the clinical study.

Thus, the assertion by the Patent Office that one or both of these papers "teach that stent grafts and stents are interchangeably used in the art to treat vascular aneurysm" (Office Action at page 3), is simply incorrect. Such a teaching is not found in Chuter *et al.* and/or May *et al.* Not surprisingly, the Patent Office has failed to identify specific language in these references, to support of its conclusory assertion that Chuter *et al.* and/or May *et al.* teach that stents and stent-grafts are interchangeable (*Id.*).

[5] For the purposes of this argument, the Evans reference will be ignored, since it was used by the Patent Office merely to show assemblage and use of a 'kit' for vascular repair (Office Action at page 3). Appellants submit that the combination of McCrory *et al.*, Chuter *et al.*, and May *et al.* do not produce the underlying invention claimed in "kit" form. Note that the Patent Office has conceded that Evans does not teach the use of stent-grafts (page 6).

Since the obviousness rejection relies on incorrect assertions relating to the alleged teaching in the clinical papers, Appellants submit that the Patent Office has failed to make a case for obviousness. For at least this reason, Appellants respectfully request withdrawal of the rejection.

B. One skilled in the art would not be motivated to combine Chuter *et al.* and/or May *et al.* with McCrory.

It is well-established patent law that to establish a *prima facie* case for obviousness, under 35 U.S.C. § 103, there must be (i) some suggestion or motivation to combine the references, (ii) a reasonable expectation of success, and (iii) the prior art must teach each and every limitation of the claims under examination. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Therefore, even if, *arguendo*, the Chuter *et al.* or the May *et al.* references, taken separately or together, suggested that stents and stent-grafts were equivalent in the art, this observation, by itself, would be insufficient to support a prima facie obviousness rejection under *In re Vaeck*. To support an obviousness rejection in the instant case, Chuter *et al.* and May *et al.*, taken separately or together, must teach that *stent-grafts* are interchangeable with *stents* for use in endovascular aneurysm repair AND provide motivation to combine their teachings with the McCrory patent, which teaches vascular occlusive systems involving a stent and a polymeric composition. Only if both conditions are met could the resulting combination yield a method of endovascular aneurysm repair involving *stent-grafts* and polymeric compositions.

However, neither the Chuter *et al.* and/or the May *et al.* reference provides any motivation to be combined with the teachings of McCrory. Chuter *et al.* and May *et al.* are merely clinical studies involving populations of patients that underwent endovascular aneurysm repair, involving stent-grafts. The studies are almost purely descriptive and focus primarily on study methodology and statistical analyses, while providing little critical analysis of the

underlying methods and devices used for endovascular repair.[6] Importantly, neither study appears to discuss polymeric compositions for use with stent-grafts; therefore, there is no logical nexus between the Chuter *et al.* and/or May *et al.* clinical studies and the invention disclosed in the McCrory patent.

Accordingly, there is no motivation to combine the references cited in support of the outstanding obviousness rejection. Under the standard set forth in *In re Vaeck*, discussed above, the Patent Office has failed to establish a *prima facie* case for obviousness for Appellants to rebut and the rejection should be withdrawn.

CONCLUSION

In view of the above arguments, Appellants submit that withdrawal of the outstanding obviousness rejection is in order. The rejection is factually/scientifically flawed because the contents of the Chuter *et al.* and/or May *et al.* references do not suggest that *stents* and *stent-grafts* are interchangeable devices. The rejection is legally flawed because, regardless of any inferences the Patent Office appears to have drawn from the clinical studies of Chuter *et al.* and/or May *et al.*, there is no motivation to combine these references with the teachings of McCrory. Lastly, the Patent Office has improperly asserted Chuter *et al.* and/or May *et al.* as prior art references when support for the pending claims is found in the ultimate parent application, which antedates the clinical studies cited as prior art references.

For at least these reasons, Appellants respectfully request withdrawal of the outstanding obviousness rejection.

[6] Appellants do not intend to denigrate these clinical studies. Nonetheless, the concluding paragraphs of both studies (Chuter *et al.* at page 131 and May *et al.* at page 129) make self-evident the dearth of meaningful analysis contained within.

37 C.F.R. § 41.37(c)(1)(viii) CLAIMS APPENDIX

16. A kit of parts for use in sealing endoleaks arising from endovascular repair of an aneurysm which comprises:

(a) a fluid composition which forms a coherent mass in the presence of blood which mass adheres to the vascular surface and/or the surface of the endovascular prosthesis wherein said fluid composition comprises a biocompatible solvent and a biocompatible polymer;

(b) a catheter suitable for delivering the fluid composition to an endoleak site formed from endovascular repair of an abdominal aortic aneurysm;

(c) a catheter suitable for delivering an endovascular prosthesis to the aneurysm; and

(d) an endovascular prosthesis comprising a stent graft capable of inhibiting but not completely arresting blood flow into the abdominal aortic aneurysm due to the presence of one or more endoleaks.

20. The kit of parts according to Claim 16 wherein said biocompatible polymer is selected from the group consisting of cellulose acetate polymers, ethylene vinyl alcohol copolymers and polyacrylates.

21. The kit of parts according to Claim 20 wherein said biocompatible polymer is a cellulose acetate polymer or an ethylene vinyl alcohol copolymer.

22. The kit of parts according to Claim 16 wherein said biocompatible solvent is selected from the group consisting of dimethylsulfoxide, ethanol, ethyl lactate, and acetone.

23. the kit of parts according to Claim 22 wherein said biocompatible solvent is dimethylsulfoxide.

24. The kit of parts according to Claim 16 wherein the fluid composition further comprises a contrast agent.

25. The kit of parts according to Claim 24 wherein said contrast agent is a water insoluble contrast agent.

26. The kit of parts according to Claim 25 wherein said water insoluble contrast agent is selected from the group consisting of tantalum, tantalum oxide, tungsten, and barium sulfate.

27. The kit of parts according to Claim 25 wherein said water insoluble contrast agent is characterized by having an average particle size of about 10 μm or less.

28. The kit of parts according to Claim 24 wherein said contrast agent is a water soluble contrast agent.

29. The kit of parts according to Claim 28 wherein said water soluble contrast agent is selected from the group consisting of metrizamide, iopamidol, iothalamate sodium, iodomide sodium, and meglumine.

30. The kit of parts according to Claim 24 which further comprises:

(e) a contrast agent dissolved in saline.

31. The kit of parts according to Claim 30 wherein the contrast agent is iopamidol.

32. The kit of parts according to Claim 16 wherein said one or more endoleaks arises from incomplete sealing at the interface of the aortic wall and the end of the prosthesis or from defects within the endovascular prosthesis.

37 C.F.R. § 41.37(c)(1)(ix) EVIDENCE APPENDIX

The following evidentiary documents are attached hereto:

A. Parodi, J.C. (1998) Endovascular AAA stent grafts: technology, training and proper patient selection. *JPVA*. 1.1-1.2. Reference No. 17 at page 3 of the subject application. This reference was incorporated by reference in its entirety into U.S. Patent Application Serial No. 09/273,120, now U.S. Patent No. 6,203,779, which is the "grandparent" of the subject application.

B. Declaration of Richard Greff. Made of record January 22, 2003.

C. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). First referred to in Appellants' Reply and Amendment of January 20, 2004.

37 C.F.R. § 41.37(c)(1)(x) RELATED PROCEEDINGS APPENDIX

There are no related proceedings

Respectfully submitted,

Date: September 30, 2005

By _____

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Technology, Training and Proper Patient Selection

Juan C. Parodi, M.D.
Combined Session: Vascular Surgery and Interventional Radiology

Medical Industries finally got involved in the stent-graft technology, probably they started to learn the impact of these new methods on the vascular diseases' therapy arena. Use of home made systems are currently generally restricted to those cases with a very unusual anatomy that are not suitable for the use of any device produced by the industry.

Thin resistant vascular fabric grafts have been developed and most of the companies incorporated those very thin graft in their products. These thin grafts allowed the practitioners to use low profile devices. Polyester woven grafts were the favorites; PTFE has been used in some devices but to obtain the thickness utilized in the Polyester fabric graft, the resistance to dilatation had to be compromised.

Different metal components of devices blended with fabric grafts resulted in modular systems adaptable to most of the anatomical variations of aneurysms.

Tubular devices are seldom used for AAA since mid and long term results using them have been unacceptable. The aorto-bi-iliac configuration is by far the favorite one. Aorto-uni-iliac device finds application in some complicated cases with unfavorable anatomy to apply the bifurcated configuration.

Nitinol (Nickel-Titanium Alloy) is the stent component more popular among devices. The super-elastic and the nitinol with thermal memory are the two types utilized.

Some devices place the graft inside the metallic frame (AneuRx, Talent), some others on the inside (Vanguard). In theory to have the graft inside has advantage over the other because the inner surface is smoother and less prone to form thrombus.

Crossing the renal arteries ostium appears as a valuable alternative to be used in clinical cases in which the proximal neck is short. It is well known that the wall strength of the aorta at the level of the branches is stronger due to the presence of intercrossing adventitial fibers that come from the branches, in this case the renal arteries. Few cases of renal artery embolization and occlusion were reported but appears that for most of the cases the technique is safe. It is expected however that special bare stent configurations could be developed by the Medical Industries for those cases in which the renal arteries will be covered by the stent.

Balloon expandable stents were the first utilized in this field, balloon rupture and balloon displacement with flow and pressure made those systems more cumbersome than the self expandable, spring loaded stents. Material fatigue has been an issue brought by the follow up studies, hook fracture happened as well as suture breakage. Those problems have been addressed and for the most part solved by the industry.

Development of co-extruded systems are in process. They will have several advantages in terms of avoiding the "wind sock effect" in the moment of deployment. This new systems in which the stent is introduced in a different sheath than the graft provides the solution to flow interruption during deployment. Blood flow passes through the interstices foe the stent while the system is deployed. This system is expected to be very useful to treat thoracic aortic aneurysms and dissections.

Endosutures have also been developed. They could be used in cases of short and dilated necks. Testing will disclose its long term durability. Method of "endosuturing" is described in a different presentation of this meeting.

Training

In vitro flow models allow appropriate training for interventionists, they are more practical than the animal models. Training using human cadavers provide a closer to the reality scenario. Assisting experienced surgeons in several cases and having expert persons assisting the beginners on their first cases completes an acceptable method of training.

Endoluminal treatment of AAA is not a simple procedure, it is not reasonable to start doing complex endovascular procedures before grad-

ually being involed in progressively more technically demanding procedures. It is advisable for the surgeons to gain experience with guidewires, catheters and introducer sheaths doing diagnostic procedures first, the second step is to do simple iliac or superficial femoral arteries and angioplasties, to deploy inferior Vena Cava filters and to use some balloon expandable and self expandable stents before embarking in endoluminal treatment of AAA. Surgical Societies are in the process of regulating Credentials to insure appropriate application of this new technology.

Patient Selection

Endoluminal treatment of AAA is still an experimental procedure, thus, the two main application of the method are: Patients included in a clinical trial and patients with large aneurysms considered to be in the group of prohibitive risk to have the standard open procedure.

Proper patient selection results in excellent results in centers with extensive experience on using endovascular treatment of AAA. After gaining experience some centers have embarked in the treatment of more complex patients and anatomical situations.

Essentially a good candidate for this technique is a patient with an AAA otherwise healthy, not very obese with straight arteries, proximal neck of 2 cm or more, common iliac arteries of more than 7mm and less than 11mm in diameter. No stenosis or occlusion of the iliac axis. Some systems tolerate small angulations (less than 60 degrees) of the proximal neck. Tortuosity of the iliac arteries can be handled by the "pull down technique" described by us, the use of stiff wires and the application of a through and through guidewire inserted from the brachial artery down to the femoral artery, applying gentle tension to the wire usually straightens the iliac axis. Heavily calcified tortuous arteries are still a challenge for accessing the aorta. Lower profile and more flexible systems have helped to overcome some of those difficult situations, if the indication is sound, facing a serious problem of access can be solved by creating a temporary access implanting a graft onto the common iliac artery bringing the other end to the inguinal area.

In centers with a large experience, patients with unfavorable anatomy can be treated with reasonable success rate. Those indications, however, should be made with great caution, aneurysms should be large enough or even symptomatic to insure that the risk/benefit ratio justifies the endoluminal treatment.

Some patients face more risk of embolization during endoluminal treatment of AAAs, those are patients who had spontaneous embolization in the past, irregular surface of mural thrombus on the CT Scan or double lumen of the aorta. This group of patients should be treated using a different technique. Acess is gained from the brachial artery using a 6Fr. Introducer. A long 4 Fr Swan-Ganz is inserted into the brachial artery and advanced into the thoracic aorta, the balloon is inflated and the balloon is let to navigate with flow, the abdominal aorta is reached and without disturbing the thrombus the balloon is retrieved from the femoral arteriotomy and an extra-still guidewire inserted creating a through and through wire connection from the brachial artery to the femoral artery, in this way penetration of the wire into the thrombus is prevented diminishing the risk of embolization caused by disruption of the thrombus.

NOTES

Patent
Attorney's Docket No. 018413-378

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	**BOX AF**
	)	
Charles RICCI *et al.*	)	Group Art Unit: 1617
	)	
Application No.: 09/954,789	)	Examiner: Shahnam J. Sharareh
	)	
Filed: September 12, 2001	)	
	)	
For: METHODS FOR TREATING ENDOLEAKS DURING ENDOVASCULAR REPAIR OF ABDOMINAL AORTIC ANEURYSMS	)	

DECLARATION OF RICHARD J. GREFF PURSUANT TO 37 C.F.R. §1.132

The Assistant Commissioner for Patents
Washington, D.C. 20231
BOX AF

Sir:

I, RICHARD J. GREFF, hereby declare:

1. I am a joint inventor for the above-noted application.

2. In 1970, I received a Ph.D. in Polymer Chemistry from Polytechnic University, New York. I have more than thirty years experience in polymer chemistry, including over twenty-five years experience with medical devices and over eight years experience with the preparation and use of embolic compositions. I also have experience with the *in vivo* use in animals of embolic compositions and medical devices used to treat aneurysms.

3. I currently work as a consultant to several biomedical companies, and one of the companies I consult for is Micro Therapeutics, Inc., assignee of the entire right, title, and interest in this application.

4. I am familiar with the final Office Action received in the above-noted application and with the claimed invention. Specifically, I am aware that kits of parts comprising: (a) fluid compositions, (b) a catheter suitable for delivery of the fluid composition, (c) a catheter suitable for delivery of an endovascular prosthesis, and (d) an endovascular prosthesis comprising a stent graft capable of inhibiting blood flow into an abdominal aortic aneurysm are claimed.

5. I was present during the personal Interview with Examiner Sharareh conducted by Gerald F. Swiss, Esq. (Reg. No. 30,113) and Erin M. Dunston (Reg. No. 51,147) on December 4, 2002, concerning the final Office Action received in this application. At the Interview, Examiner Sharareh expressed concern that the claimed prosthesis is the same as that found in the publications cited in his Official Actions to reject the claims. Mr. Swiss, Mrs. Dunston, and I explained that the claimed stent graft prosthesis is *not* the same as the vascular stents or vascular grafts found in the cited publications: U.S. Patent No. 5,702,361 to Evans, U.S. Patent No. 5,443,454 to Tanabe, U.S. Patent No. 5,749,894 to Engelson, and U.S. Patent No. 5,695,480 to

Evans. I offered to submit a Declaration, based upon my experience in the field of vascular devices to treat aneurysms, explaining the difference between vascular stents, vascular grafts, and the claimed stent grafts. This is that Declaration.

6. **Vascular Stents** are cylindrical devices that are placed intraluminally to support and keep open a vascular (arterial) blood vessel. Vascular stents are most often constructed of metals (such as stainless steel, tantalum, and nitinol) for strength and flexibility, and are designed to have an open structure (such as mesh, ring, coil, and slotted tube) with a low metal to exposed artery ratio (less than 20%) to prevent occlusion and/or damage to the vascular wall. Stents are delivered intraluminally, usually over a catheter, and are positioned by balloon expansion or are self-expanding.

7. **Vascular Grafts** are natural (such as autologous saphenous vein and bovine carotid heterograft) or synthetic (such as Dacron or polytetrafluoroethylene ("PTFE")), tubular replacements for vascular (arterial) repair or replacement. Dacron grafts are woven or knitted, whereas PTFE grafts are biaxially stretched to produce a fibrilliar microstructure. Vascular grafts are closed or impermeable, to prevent blood leakage. Vascular grafts are attached by suture in an open surgical procedure.

8. In contrast to either vascular stents or vascular grafts, **Stent Grafts** are combination devices that contain a vascular graft to repair or replace the diseased blood vessel, and stents for fixation and sealing of the ends of the device, intraluminally. Stent grafts are most successful in the treatment of AAA disease. Stent grafts are placed intraluminally over a catheter and anchored in the blood vessel by expansion (balloon expansion or self-expansion) of the stent portions of the device. The graft portion contains the blood flow and excludes the diseased portion of the blood vessel. The graft portion is constructed of known materials (Dacron polyester), with more recent designs containing additional support/anchoring structures. The sealing stent ends of the stent graft may contain supplemental anchoring devices, such as hooks or barbs. Stent grafts come in several configurations, including straight, tapered, or bifurcated. Stent grafts may be referred to as endovascular grafts because of the nature of their placement.

9. The distinctions between and among vascular stents, vascular grafts, and stent grafts was known to one of skill in the art at the time Applicants' invention was made. These distinctions are explained in a number of publications, which are being submitted as attachments to this Declaration. The enclosed publications may be categorized as follows:

Vascular Stents:

i. STEDMAN'S MEDICAL DICTIONARY, 27th Edition, Lippincott Williams & Wilkins, eds., 2000, Page 1696.

ii. DORLAND'S ILLUSTRATED MEDICAL DICTIONARY, 29th Edition, W.B. Saunders Co., 2000, Page 1698.

iii. *Selection of Coronary Stents*, A. Colombo *et al.*, 40(6) J. AM. COLLEGE OF CARDIOLOGY 1021-1033.

iv. *Stents for Intracoronary Placement: Current Status and Future Directions*, E. Eeckhout *et al.*, 27(4) J.A.C.C. 757-765.

Vascular Grafts:

i. The Biomedical Engineering Handbook, Chapter 124, "Vascular Grafts," D. Nu & R. Allen, Pages 1871-1878, CRC Press, 1995.

Stent Grafts:

i. *Endovascular Stent Grafts: Technology, Training and Proper Patient Selection, Combined Session: Vascular Surgery and Interventional Radiology*, J. Parodi, J.P.V.A. 1.1-1.2

ii. *Endoleak after stent-graft treatment of abdominal aortic aneurysm: a meto-analysis of clinical studies*, G.W.H. Schurink *et al.*, 86 BRITISH J. SURGERY 581-587, 1999.

iii. *Endovascular Management of "Endoleaks" After Transluminal Infrarenal Abdominal Aneurysm Repair*, T. J. Hölzenbein *et al.*, 16 EUR. J. VASC. ENDOVASC. SURG. 208-217, 1998.

iv. *Comparison of first- and second- generation prostheses for endoluminal repair of abdominal aortic aneurysms: A 6-year study with life table analysis*, J. May *et al.*, 32(1) J. VASCULAR SURGERY 124-129, 2000.

v. *Embolotherapy of Persistent Endoleaks after Andovascular Repair of Abdominal Aortic Aneurysm with the Ancure-Endovascular Technologies Endograft System*, N. Amesur *et al.*, 10(9) J.V.I.R.1175-1182, 1999.

vi. *Endoluminal repair of infrarenal abdominal aortic aneurysms using a modular stent-graft: one-year clinical results from a European multicentre trial*, R. P. Tutein Nolthenius *et al.*, 7(5) CARDIOVASCULAR SURGERY 503-507, 1999.

vii. *Endovascular aneurysm repair in high-risk patients*, T. A.M. Chuter *et al.*, 31(1:1) J. VASCULAR SURGERY 122-133, 2000.

viii. *AneuRx stent graft versus open surgical repair of abdominal aortic aneursyms: Multicenter prospective clinical trial*, C. K. Zarins *et al.*, 29(2) J. VASCULAR SURGERY 292-308, 1999.

ix. *Realistic Expectations for Patients with Stent-graft Treatment of Abdominal Aortic Aneurysms. Results of a European Multicentre Registry*, Ph. Cuypers *et al.*, 17 EUR J. VASC. ENDOVASC. SURG. 507-516, 1999.

x. *Endoluminal abdominal aortic aneurysm surgery*, K.R. Woodburn *et al.*, 85 BRITISH J. SURGERY 435-443, 1998.

Wallstent and Wallgraft:

i. *Biocompatibility and Performance of the Wallstent and the Wallgraft, Jostent, and Hemobahn Stent-Grafts in a Sheep Model*, M. Cejna *et al.*, 13(8) J.V.I.R. 823-830, 2002.

10. One publication, "*Biocompatibility and Performance of the Wallstent and the Wallgraft, Jostent, and Hemobahn Stent-Grafts in a Sheep Model,*" by M. Cejna *et al.*, provides an excellent description of stent grafts, as it describes an *in vivo* comparison of three stent grafts. Specifically mentioned in this publication is a Wallgraft, a type of stent graft. *See Page 824, Description of Figure 1, of the Cejna publication*. Wallgraft, stent graft, and Wall stent graft (as mentioned in Applicants' Example 3, at Page 27 of the application) are synonyms.

11. Based on both the content of the publications cited above and my personal experience, it is my opinion that stent grafts are their own entities, and may not be considered as either vascular stents or vascular grafts. The differences between and among vascular stents, vascular grafts, and stent grafts is know throughout the art.

12. I hereby declare that all statements made herein are of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 1/22/03

Richard J. Greff, Ph.D.

In re Vaeck

U.S. Court of Appeals Federal Circuit
20 USPQ2d 1438

Decided October 21, 1991
No. 91-1120

Headnotes

PATENTS

1. Patentability/Validity - Obviousness - Combining references (§ 115.0905)

Rejection of claimed subject matter as obvious under 35 USC 103 in view of combination of prior art references requires consideration of whether prior art would have suggested to those of ordinary skill in art that they should make claimed composition or device, or carry out claimed process, and whether prior art would also have revealed that such person would have reasonable expectation of success; both suggestion and reasonable expectation of success must be founded

in prior art, not in applicant's disclosure.

2. Patentability/Validity - Obviousness - Relevant prior art - Particular inventions (§ 115.0903.03)

Patent and Trademark Office has failed to establish prima facie obviousness of claims for use of genetic engineering techniques for producing proteins that are toxic to insects such as larvae of mosquitos and black flies, since prior art does not disclose or suggest expression in cyanobacteria of chimeric gene encoding insecticidally active protein, or convey to those of ordinary skill reasonable expectation of success in doing so; expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious expression of unrelated genes in cyanobacteria for unrelated purposes.

3. Patentability/Validity - Specification - Enablement (§ 115.1105)

JUDICIAL PRACTICE AND PROCEDURE

Procedure - Judicial review - Standard of review - Patents (§ 410.4607.09)

Specification must, in order to be enabling as required by 35 USC 112, first paragraph, teach person skilled in art to make and use invention without "undue experimentation," which does not preclude some experimentation; enablement is question of law which is reviewed independently on appeal, although such determination is based upon underlying factual findings which are reviewed for clear error.

PATENTS

4. Patentability/Validity - Specification - Enablement (§ 115.1105)

Patent and Trademark Office did not err in rejecting, as non-enabling pursuant to 35 USC 112, first paragraph, claims for use of genetic engineering techniques for producing proteins that are toxic to insects such as larvae of mosquitos and black flies, in view of relatively incomplete understanding of biology of cyanobacteria as of applicants' filing date, as well as limited disclosure by applicants of particular cyanobacterial genera operative in claimed invention, since there is no reasonable correlation between narrow disclosure in applicants' specification and broad scope of protection sought in claims encompassing gene expression in any and all cyanobacteria.

Case History and Disposition:

Appeal from the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences.

Application for patent, serial no. 07/021,405, filed March 4, 1987, by Mark A. Vaeck, Wipa Chungjatupornchai, and Lee McIntosh (hybrid genes incorporating a DNA fragment containing a gene coding for an insecticidal protein, plasmids, transformed cyanobacteria expressing such protein and method for use as a biocontrol agent). From decision rejecting claims 1-48 and 50-52 as unpatentable under 35 USC 103, and rejecting claims 1-48 and 50-51 for lack of enablement, applicants appeal. Affirmed and part and reversed in part; Mayer, J., dissents with opinion.

Attorneys:

Ian C. McLeod, Okemos, Mich., for appellant.

Teddy S. Gron, associate solicitor (Fred E. McKelvey, solicitor and Richard E. Schafer, associate solicitor, with him on brief), for appellee.

Judge:

Before Rich, Archer, and Mayer, circuit judges.

Opinion Text

Opinion By:

Rich, J.

This appeal is from the September 12, 1990 decision of the Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board), affirming the examiner's rejection of claims 1-48 and 50-52 of application Serial No. 07/021,405, filed March 4, 1987, titled "Hybrid Genes Incorporating a DNA Fragment Containing a Gene Coding for an Insecticidal Protein, Plasmids, Transformed Cyanobacteria Expressing Such Protein and Method for Use as a Biocontrol Agent" as unpatentable under 35 USC 103, as well as the rejection of claims 1-48 and 50-51 under 35 USC 112, first paragraph, for lack of enablement. We reverse the § 103 rejection. The § 112 rejection is affirmed in part and reversed in part.

BACKGROUND

A. *The Invention*

The claimed invention is directed to the use of genetic engineering techniques 1 for production of proteins that are toxic to insects such as larvae of mosquitos and black flies. These swamp-dwelling pests are the source of numerous human health problems, including malaria. It is known that certain species of the naturally-occurring *Bacillus* genus of bacteria produce

proteins ("endotoxins") that are toxic to these insects. Prior art methods of combatting the insects involved spreading or spraying crystalline spores of the insecticidal *Bacillus* proteins over swamps. The spores were environmentally unstable, however, and would often sink to the bottom of a swamp before being consumed, thus rendering this method prohibitively expensive. Hence the need for a lower-cost method of producing the insecticidal *Bacillus* proteins in high volume, with application in a more stable vehicle.
As described by appellants, the claimed subject matter meets this need by providing for the production of the insecticidal *Bacillus* proteins within host cyanobacteria. Although both cyanobacteria and bacteria are members of the procaryote 2 kingdom, the

cyanobacteria (which in the past have been referred to as "blue-green algae") are unique among procaryotes in that the cyanobacteria are capable of oxygenic photosynthesis. The cyanobacteria grow on top of swamps where they are consumed by mosquitos and black flies. Thus, when *Bacillus* proteins are produced within transformed 3 cyanobacterial hosts according to the claimed invention, the presence of the insecticide in the food of the targeted insects advantageously guarantees direct uptake by the insects.
More particularly, the subject matter of the application on appeal includes a chimeric (i.e., hybrid) gene comprising (1) a gene derived from a bacterium of the *Bacillus* genus whose product is an insecticidal protein, united with (2) a DNA promoter effective for expressing 4 the *Bacillus* gene in a host cyanobacterium, so as to produce the desired insecticidal protein.
The claims on appeal are 1-48 and 50-52, all claims remaining in the application. Claim 1 reads:
1. A chimeric gene capable of being expressed in Cyanobacteria cells comprising:
(a) a DNA fragment comprising a promoter region which is effective for expression of a DNA fragment in a Cyanobacterium; and
(b) at least one DNA fragment coding for an insecticidally active protein produced by a Bacillus strain, or coding for an insecticidally active truncated form of the above protein or coding for a protein having substantial sequence homology to the active protein,
the DNA fragments being linked so that the gene is expressed.
Claims 2-15, which depend from claim 1, recite preferred *Bacillus* species, promoters, and selectable markers. 5 Independent claim 16 and claims 17-31 which depend therefrom are

directed to a hybrid plasmid vector which includes the chimeric gene of claim 1. Claim 32 recites a bacterial strain. Independent claim 33 and claims 34-48 which depend therefrom recite a cyanobacterium which expresses the chimeric gene of claim 1. Claims 50-51 recite an insecticidal composition. Claim 52 recites a particular plasmid that appellants have deposited.

B. *Appellants' Disclosure*

In addition to describing the claimed invention in generic terms, appellants' specification discloses two particular species of *Bacillus* (*B. thuringiensis, B. sphaericus*) as sources of insecticidal protein; and nine genera of cyanobacteria (*Synechocystis, Anacystis, Synechococcus, Agmenellum, Aphanocapsa, Gloecapsa, Nostoc, Anabaena* and *Ffremyllia*) as useful hosts.

The working examples relevant to the claims on appeal detail the transformation of a single strain of cyanobacteria, i.e., *Synechocystis* 6803. In one example, *Synechocystis* 6803 cells are transformed with a plasmid comprising (1) a gene encoding a particular insecticidal protein ("B.t. 8") from *Bacillus thuringiensis* var. *israelensis,* linked to (2) a particular promoter, the P $_L$promoter from the bacteriophage Lambda (a virus of *E. coli*). In another example, a different promoter, i.e., the *Synechocystis* 6803 promoter for the rubisco operon, is utilized instead of the Lambda P $_L$promoter.

C. *The Prior Art*

A total of eleven prior art references were cited and applied, in various combinations, against the claims on appeal.

The focus of Dzelzkalns, 6 the primary reference cited against all of the rejected claims, is to determine whether chloroplast promoter sequences can function in cyanobacteria. To that end Dzelzkalns discloses the expression in cyanobacteria of a chimeric gene comprising a chloroplast promoter sequence fused to a gene encoding the enzyme chloramphenicol acetyl transferase (CAT). 7 Importantly, Dzelzkalns teaches the use of the CAT gene as a "marker" gene; this use of antibiotic resistance-conferring genes for selection purposes is a common technique in genetic engineering.

Sekar I, 8 Sekar II, 9 and Ganesan 10 collectively disclose expression of genes encoding certain *Bacillus* insecticidal proteins in the bacterial hosts *B. megaterium, B. subtilis* and *E. coli.*
Friedberg 11 discloses the transformation of the cyanobacterium *Anacystis nidulans* R2 by a plasmid vector comprising the O $_L$P $_L$operator-promoter region and a temperature-sensitive repressor gene of the bacteriophage Lambda. While the cyanobacteria are attractive organisms for the cloning of genes involved in photosynthesis, Friedberg states, problems may still be encountered such as suboptimal expression of the cloned gene, detrimental effects on cell growth of overexpressed, highly hydrophobic proteins, and rapid turnover of some gene products. To address these problems, Friedberg teaches the use of the disclosed Lambda regulatory signals in plasmid vehicles which, it states, have "considerable potential for use as vectors the expression of which can be controlled in *Anacystis* ...."
Miller 12 compares the initiation specificities *in vitro* of DNA-dependent RNA polymerases 13 purified from two different species of cyanobacteria (*Fremyella diplosiphon* and *Anacystis nidulans*), as well as from *E. coli.*
Nierzwicki-Bauer 14 identifies in the cyanobacterium *Anabaena* 7120 the start site for transcription of the gene encoding *rbc* L, the large subunit of the enzyme ribulose-1, 5-bisphosphate carboxylase. It reports that the nucleotide sequence 14-8 base pairs preceding the transcription start site "resembles a good *Escherichia coli* promoter," but that the sequence 35 base pairs before the start site does not.
Chauvat 15 discloses host-vector systems for gene cloning in the cyanobacterium *Synechocystis* 6803, in which the antibiotic resistance-conferring *neo* gene is utilized as a selectable marker.
Reiss 16 studies expression in *E. coli* of various proteins formed by fusion of certain foreign DNA sequences with the *neo* gene.
Kolowsky 17 discloses chimeric plasmids designed for transformation of the cyanobacterium *Synechococcus* R2, comprising an antibiotic-resistant gene linked to chromosomal DNA from the *Synechococcus* cyanobacterium.
Barnes, United States Patent No. 4,695,455, is directed to the treatment with stabilizing chemical reagents of pesticides produced by expression of heterologous genes (such as those encoding *Bacillus* proteins) in host microbial cells such as *Pseudomonas* bacteria. The host cells are

killed by this treatment, but the resulting pesticidal compositions exhibit prolonged toxic activity when exposed to the environment of target pests.

D. *The Grounds of Rejection*

1. The § 103 Rejections

Claims 1-6, 16-21, 33-38, 47-48 and 52 (which include all independent claims in the application) were rejected as unpatentable under 35 USC 103 based upon Dzelzkalns in view of Sekar I or Sekar II and Ganesan. The examiner stated that Dzelzkalns discloses a chimeric gene capable of being highly expressed in a cyanobacterium, said gene comprising a promoter region effective for expression in a cyanobacterium operably linked to a structural gene encoding CAT. The examiner acknowledged that the chimeric gene and transformed host of Dzelzkalns differ from the claimed invention in that the former's structural gene encodes CAT rather than insecticidally active protein. However, the examiner pointed out, Sekar I, Sekar II, and Ganesan teach genes encoding insecticidally active proteins produced by *Bacillus,* and the advantages of expressing such genes in heterologous 18 hosts to obtain larger quantities of the protein. The examiner contended that it would have been obvious to one of ordinary skill in the art to substitute the *Bacillus* genes taught by Sekar I, Sekar II, and Ganesan for the CAT gene in the vectors of Dzelzkalns in order to obtain high level expression of the *Bacillus* genes in the transformed cyanobacteria. The examiner further contended that it would have been obvious to use cyanobacteria as heterologous hosts for expression of the claimed genes due to the ability of cyanobacteria to serve as transformed hosts for the

expression of heterologous genes. In the absence of evidence to the contrary, the examiner contended, the invention as a whole was prima facie obvious.

Additional rejections were entered against various groups of dependent claims which we need not address here. All additional rejections were made in view of Dzelzkalns in combination with Sekar I, Sekar II, and Ganesan, and further in view of other references discussed in Part C above. The Board affirmed the § 103 rejections, basically adopting the examiner's Answer as its opinion while adding a few comments. The legal conclusion of obviousness does not require absolute

certainty, the Board added, but only a reasonable expectation of success, citing *In re O'Farrell,* 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988). In view of the disclosures of the prior art, the Board concluded, one of ordinary skill in the art would have been motivated by a reasonable expectation of success to make the substitution suggested by the examiner.

2. The § 112 Rejection

The examiner also rejected claims 1-48 and 50-51 under 35 USC 112, first paragraph, on the ground that the disclosure was enabling only for claims limited in accordance with the specification as filed. Citing *Manual of Patent Examining Procedure* (MPEP) provisions 706.03(n) 19 and (z) 20 as support, the examiner took the position that undue experimentation would be required of the art worker to practice the claimed invention, in view of the unpredictability in the art, the breadth of the claims, the limited number of working examples and the limited guidance provided in the specification. With respect to unpredictability, the examiner stated that

he cyanobacteria comprise a large and diverse group of photosynthetic bacteria including large numbers of species in some 150 different genera including *Synechocystis, Anacystis, Synechococcus, Agmenellum, Nostoc, Anabaena,* etc. The molecular biology of these organisms has only recently become the subject of intensive investigation and this work is limited to a few genera. Therefore the level of unpredictability regarding heterologous gene expression in this large, diverse and relatively poorly studied group of procaryotes is high....

The Board affirmed, noting that "the limited guidance in the specification, considered in light of the relatively high degree of unpredictability in this particular art, would not have enabled one having ordinary skill in the art to practice the broad scope of the claimed invention without undue experimentation. *In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970)."

OPINION

A. *Obviousness*

We first address whether the PTO erred in rejecting the claims on appeal as prima facie obvious within the meaning of 35 USC 103. Obviousness is a legal question which this court independently reviews, though based upon underlying factual findings which we review under the clearly erroneous standard. *In re Woodruff,* 919 F.2d 1575, 1577, 16 USPQ2d 1934, 1935

(Fed. Cir. 1990).

[1] Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia,* consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.*

[2] We agree with appellants that the PTO has not established the prima facie obviousness of the claimed subject matter. The prior art simply does not disclose or suggest the expression in cyanobacteria of a chimeric gene encoding an insecticidally active protein, or convey to those of ordinary skill a reasonable expectation of success in doing so. More particularly, there is no suggestion in Dzelzkalns, the primary reference cited against all claims, of substituting in the disclosed plasmid a structural gene encoding *Bacillus* insecticidal proteins for the CAT gene utilized for selection purposes. The expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria for unrelated purposes.

The PTO argues that the substitution of insecticidal *Bacillus* genes for CAT marker genes in cyanobacteria is suggested by the secondary references Sekar I, Sekar II, and Ganesan, which collectively disclose expression of genes encoding *Bacillus* insecticidal proteins in two species of host *Bacillus* bacteria (*B. megaterium* and *B. subtilis*) as well as in the bacterium *E. coli.* While these references disclose expression of *Bacillus* genes encoding insecticidal proteins in certain transformed *bacterial* hosts, nowhere do these references disclose or suggest expression of such genes in transformed *cyanobacterial* hosts.

To remedy this deficiency, the PTO emphasizes similarity between bacteria and cyanobacteria, namely, that these are both procaryotic organisms, and argues that this fact would suggest to those of ordinary skill the use of cyanobacteria as hosts for expression of the claimed chimeric

genes. While it is true that bacteria and cyanobacteria are now both classified as procaryotes, that fact alone is not sufficient to motivate the art worker as the PTO contends. As the PTO concedes, cyanobacteria and bacteria are not identical; they are classified as two separate divisions of the kingdom Procaryotae. 21 Moreover, it is only in recent years that the biology of cyanobacteria has been clarified, as evidenced by references in the prior art to "blue-green algae." Such evidence of recent uncertainty regarding the biology of cyanobacteria tends to rebut, rather than support, the PTO's position that one would consider the cyanobacteria effectively interchangeable with bacteria as hosts for expression of the claimed gene.

At oral argument the PTO referred to additional secondary references, not cited against any independent claim (i.e., Friedberg, Miller, and Nierzwicki-Bauer), which it contended disclose certain amino acid sequence homology between bacteria and cyanobacteria. The PTO argued that such homology is a further suggestion to one of ordinary skill to attempt the claimed invention. We disagree. As with the Dzelzkalns, Sekar I, Sekar II, and Ganesan references discussed above, none of these additional references disclose or suggest that cyanobacteria could serve as hosts for expression of genes encoding *Bacillus* insecticidal proteins. In fact, these additional references suggest as much about *differences* between cyanobacteria and bacteria as they do about similarities. For example, Nierzwicki-Bauer reports that a certain nucleotide sequence (i.e., the -10 consensus sequence) in a particular cyanobacterium resembles an *E. coli* promoter, but that another nearby nucleotide sequence (the -35 region) does not. While Miller speaks of certain promoters of the bacteriophage Lambda that are recognized by both cyanobacterial and *E. coli* RNA polymerases, it also discloses that these promoters exhibited differing strengths when exposed to the different polymerases. Differing sensitivities of the respective polymerases to an inhibitor are also disclosed, suggesting differences in the structures of the initiation complexes.

The PTO asks us to agree that the prior art would lead those of ordinary skill to conclude that cyanobacteria are attractive hosts for expression of any and all heterologous genes. Again, we can not. The relevant prior art does indicate that cyanobacteria are attractive hosts for expression of both native and heterologous *genes involved in photosynthesis* (not surprisingly, for the capability of undergoing oxygenic photosynthesis is what makes the cyanobacteria unique among procaryotes). However, these references do not suggest that cyanobacteria would be equally attractive hosts for expression of *unrelated* heterologous genes, such as the claimed genes encoding *Bacillus* insecticidal proteins.

In *O'Farrell,* this court affirmed an obviousness rejection of a claim to a method for

producing a "predetermined protein in a stable form" in a transformed bacterial host. 853 F.2d at 895, 7 USPQ2d at 1674. The cited references included a prior art publication (the Polisky reference) whose three authors included two of the three coinventor-appellants. The main difference between the prior art and the claim at issue was that in Polisky, the heterologous gene was a gene for ribosomal RNA, while the claimed invention substituted a gene coding for a predetermined protein. *Id.* at 901, 7 USPQ2d at 1679. Although, as the appellants therein pointed out, the ribosomal RNA gene is not normally translated into protein, Polisky mentioned preliminary evidence that the transcript of the ribosomal RNA gene was translated into protein, and further predicted that if a gene coding for a protein were to be substituted, extensive translation might result. *Id.* We thus affirmed, explaining that

the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the [claimed] method could be used to make proteins.

....

... Polisky contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.

Id. at 901-02, 7 USPQ2d at 1679-80.

In contrast with the situation in *O'Farrell,* the prior art in this case offers no suggestion, explicit or implicit, of the substitution that is the difference between the claimed invention and the prior art. Moreover, the "reasonable expectation of success" that was present in *O'Farrell* is not present here. Accordingly, we reverse the § 103 rejections.

B. *Enablement*

[3] The first paragraph of 35 USC 112 requires, *inter alia,* that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without "undue experimentation." *In re Wands,* 858 F.2d 731,

737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). That *some* experimentation may be required is not fatal; the issue is whether the amount of experimentation required is "undue." *Id.* at 736-37, 8 USPQ2d at 1404. Enablement, like obviousness, is a question of law which we independently review, although based upon underlying factual findings which we review for clear error. *See id.* at 735, 8 USPQ2d at 1402.

In response to the § 112 rejection, appellants assert that their invention is "pioneering," and that this should entitle them to claims of broad scope. Narrower claims would provide no real protection, appellants argue, because the level of skill in this art is so high, art workers could easily avoid the claims. Given the disclosure in their specification, appellants contend that any skilled microbiologist could construct vectors and transform many different cyanobacteria, using a variety of promoters and *Bacillus* DNA, and could easily determine whether or not the active *Bacillus* protein was successfully expressed by the cyanobacteria.

The PTO made no finding on whether the claimed invention is indeed "pioneering," and we need not address the issue here. With the exception of claims 47 and 48, the claims rejected under § 112 are not limited to any particular genus or species of cyanobacteria. The PTO's position is that the cyanobacteria are a diverse and relatively poorly studied group of organisms, comprising some 150 different genera, and that heterologous gene expression in cyanobacteria is "unpredictable." Appellants have not effectively disputed these assertions. Moreover, we note that only one particular species of cyanobacteria is employed in the working examples of appellants' specification, and only nine genera of cyanobacteria are mentioned in the entire document.

[4] Taking into account the relatively incomplete understanding of the biology of cyanobacteria as of appellants' filing date, as well as the limited disclosure by appellants of particular cyanobacterial genera operative in the claimed invention, we are not persuaded that the PTO erred in rejecting claims 1-46 and 50-51 under § 112, first paragraph. There is no reasonable correlation between the narrow disclosure in appellants' specification and the broad scope of protection sought in the claims encompassing gene expression in any and all cyanobacteria. *See In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (the first paragraph of § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification).

22 Accordingly, we affirm the § 112 rejection as to those claims.
In so doing we do *not* imply that patent applicants in art areas currently denominated as "unpredictable" must never be allowed generic claims encompassing more than the particular species disclosed in their specification. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Angstadt,* 537 F.2d 498, 502-03, 190 USPQ 214, 218 (CCPA 1976). However, there must be sufficient disclosure, either through illustrative examples or terminology, 23 to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility. Where, as here, a claimed genus represents a diverse and relatively poorly understood group of microorganisms, the required level of disclosure will be greater than, for example, the disclosure of an invention involving a "predictable" factor such as a mechanical or electrical element. *See Fisher,* 427 F.2d at 839, 166 USPQ at 24. In this case, we agree with the PTO that appellants' limited disclosure does not enable one of ordinary skill to make and use the invention as now recited in claims 1-46 and 50-51 without undue experimentation.
Remaining dependent claim 47 recites a cyanobacterium which expresses the chimeric gene of claim 1, wherein the cyanobacterium is selected from among the genera *Anacystis* and *Synechocystis.* Claim 48, which depend from claim 47, is limited to the cyanobacterium *Synechocystis* 6803. The PTO did not separately address these claims, nor indicate why they should be treated in the same manner as the claims encompassing all types of cyanobacteria. Although these claims are not limited to expression of genes encoding particular *Bacillus* proteins, we note what appears to be an extensive understanding in the prior art of the numerous *Bacillus* proteins having toxicity to various insects. The rejection of claims 47-48 under § 112 will not be sustained.

CONCLUSION

The rejection of claims 1-48 and 50-52 under 35 USC 103 is *reversed.* The rejection of claims 1-46 and 50-51 under 35 USC 112, first paragraph, is *affirmed* and the rejection of claims 47 and 48 thereunder is *reversed.*
AFFIRMED-IN-PART, REVERSED-IN-PART

Footnotes

Footnote 1. Basic vocabulary and techniques for gene cloning and expression have been described in *In re O'Farrell,* 853 F.2d 894, 895-99, 7 USPQ2d 1673, 1674-77 (Fed. Cir. 1988), and are not repeated here.
Footnote 2. All living cells can be classified into one of two broad groups, procaryotes and eucaryotes. The procaryotes comprise organisms formed of cells that do not have a distinct nucleus; their DNA floats throughout the cellular cytoplasm. In contrast, the cells of eucaryotic organisms such as man, other animals, plants, protozoa, algae and yeast have a distinct nucleus wherein their DNA resides.
Footnote 3. "Transformed" cyanobacteria are those that have successfully taken up the foreign *Bacillus* DNA such that the DNA information has become a permanent part of the host cyanobacteria, to be replicated as new cyanobacteria are generated.
Footnote 4. "Expression" of a gene refers to the production of the protein which the gene encodes; more specifically, it is the process of transferring information from a gene (which consists of DNA) via messenger RNA to ribosomes where a specific protein is made.
Footnote 5. In the context of the claimed invention, "selectable markers" or "marker genes" refer to antibiotic-resistance conferring DNA fragments, attached to the gene being expressed, which facilitate the selection of successfully transformed cyanobacteria.
Footnote 6. *Nucleic Acids Res.* 8917 (1984).
Footnote 7. Chloramphenicol is an antibiotic; CAT is an enzyme which destroys chloramphenicol and thus imparts resistance thereto.
Footnote 8. *Biochem. and Biophys. Res. Comm.* 748 (1986).
Footnote 9. *Gene* 151 (1985).
Footnote 10. *Mol. Gen. Genet.* 181 (1983).
Footnote 11. *Mol. Gen. Genet.* 505 (1986).
Footnote 12. *J. Bacteriology* 246 (1979).
Footnote 13. RNA polymerase, the enzyme responsible for making RNA from DNA, binds at

specific nucleotide sequences (promoters) in front of genes in DNA, and then moves through the gene making an RNA molecule that includes the information contained in the gene. Initiation specificity is the ability of the RNA polymerase to initiate this process specifically at a site(s) on the DNA template.

Footnote 14. *Proc. Natl. Acad. Sci. USA* 5961 (1984).

Footnote 15. *Mol. Gen. Genet.* 185 (1986).

Footnote 16. *Gene* 211 (1984).

Footnote 17. *Gene* 289 (1984).

Footnote 18. Denotes different species or organism.

Footnote 19. MPEP 706.03(n), "Correspondence of Claim and Disclosure," provides in part:
In chemical cases, a claim may be so broad as to not be supported by [the] disclosure, in which case it is rejected as unwarranted by the disclosure....

Footnote 20. MPEP 796.03(z), "Undue Breadth," provides in part:
n applications directed to intentions in arts were the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Sol,* 1938 C.D. 723; 497 O.G. 546. This is because in arts such as chemistry it is not obvious from the disclosure of one species, what other species will work. *In re Dreshfield,* 1940 C.D. 351; 518 O.G. 255 gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." ...

Footnote 21. *Stedman's Medical Dictionary* 1139 (24th ed. 1982) (definition of "Procaryotae"). Procaryotic organisms are commonly classified according to the following taxonomic hierarchy: Kingdom; Division; Class; Order; Family; Genus; Species. 3 *Bergey's Manual of Systematic Bacteriology* 1601 (1989).

Footnote 22. The enablement rejection in this case was not based upon a post-filing date state of the art, as in *In re Hogan,* 559 F.2d 595, 605-07, 194 USPQ 527, 536-38 (CCPA 1977). *See also United States Steel Corp. v. Phillips Petroleum Co.,* 865 F.2d 1247, 1251, 9 USPQ2d 1461, 1464 (Fed. Cir. 1989) (citing *Hogan*); *Hormone Research Found., Inc. v. Genentech, Inc.,* 904 F.2d 1558, 1568-69, 15 USPQ2d 1039, 1047-48 (Fed. Cir. 1990) (directing district court, on remand, to consider effect of *Hogan* and *United States Steel* on the enablement analysis of

Fisher), *cert. dismissed,* — U.S. —, 111 S. Ct. 1434 (1991). We therefore do not consider the effect of *Hogan* and its progeny on *Fisher* 's analysis of when an inventor should be allowed to "dominate the future patentable inventions of others." *Fisher,* 427 F.2d at 839, 166 USPQ at 24. Footnote 23. The first paragraph of § 112 requires nothing more than *objective* enablement. *In re Marzocchi,* 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is irrelevant. *Id.*

Dissenting Opinion Text

Dissent By:

Mayer, J., dissenting.

An appeal is not a second opportunity to try a case or prosecute a patent application, and we should not allow parties to "undertake to retry the entire case on appeal." *Perini America, Inc. v. Paper Converting Machine Co.,* 832 F.2d 581, 584, 4 USPQ2d 1621, 1624 (Fed. Cir. 1987); *Eaton Corp. v. Appliance Valves Corp.,* 790 F.2d 874, 877, 229 USPQ 668, 671 (Fed. Cir. 1986). But that is precisely what the court has permitted here. The PTO conducted a thorough examination of the prior art surrounding this patent application and concluded the claims would have been obvious. The board's decision based on the examiner's answer which comprehensively explains the rejection is persuasive and shows how the evidence supports the legal conclusion that the claims would have been obvious. Yet, the court ignores all this and conducts its own examination, if you will, as though the examiner and board did not exist. Even if thought this opinion were more persuasive than the board's, I could not join it because it misperceives the role of the court.

The scope and content of the prior art, the similarity between the prior art and the claims, the level of ordinary skill in the art, and what the prior art teaches are all questions of fact. *Graham v. John Deere Co.,* 383 U.S. 1, 17, 148 USPQ 459, 467 (1966); *Jurgens v. McKasy,* 927 F.2d 1552, 1560, 18 USPQ2d 1031, 1037 (Fed. Cir. 1991). And "[w]here there are two permissible views of

the evidence, the factfinder's choice between them cannot be clearly erroneous." *Anderson v. City of Bessemer City,* 470 U.S. 564, 574 (1985). The mere denomination of obviousness as a question of law does not give the court license to decide the factual matters afresh and ignore the requirement that they be respected unless clearly erroneous. *In re Woodruff,* 919 F.2d 1575, 1577, 16 USPQ2d 1934, 1935 (Fed. Cir. 1990); *In re Kulling,* 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1057 (Fed. Cir. 1990). There may be more than one way to look at the prior art, but on this record we are bound by the PTO's interpretation of the evidence because it is not clearly erroneous and its conclusion is unassailable. I would affirm on that basis.

- End of Case -

AF
1617

Attorney. Docket. No. 355492-2202 IFW
Application Serial No. 09/954,789

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant: Charlie RICCI, et al.

Title: METHODS FOR TREATING ENDOLEAKS DURING ENDOVASCULAR REPAIR OF ABDOMINAL AORTIC ANEURYSMS

Appl. No.: 09/954,789

Filing Date: 9/12/2001

Examiner: S. Sharareh

Art Unit: 1617

CERTIFICATE OF MAILING
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Mail Stop Appeal Brief - Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date below.

Esther Lily C. Esguerra
(Printed Name)

(Signature)

September 30, 2005
(Date of Deposit)

SUBSTITUTE APPEAL BRIEF TRANSMITTAL

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This substitute appeal brief was requested in the Office Action dated September 23, 2005. That Office Action referenced an August 16, 2005 Order issued by the USPTO Board of Appeals and Interferences which declared the original appeal brief to be defective for not complying with 37 CFR 41.37. This substitute brief complies with that Regulation.

The appeal brief fee was filed with the original appeal brief on November 22, 2004. If that fee is insufficient, please charge any deficiency to deposit account 50-0872.

Respectfully submitted,

Date: September 30, 2005

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